694. *Chemistry of New Zealand* Melicope *Species. Part VII.* Some Observations on the Relation between the Constitution of Some Flavonol Derivatives and their Acidity, Basicity, Colours with Ferric Chloride, and Ultra-violet Absorption Spectra.*

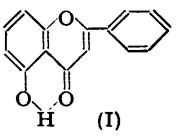
By Lindsay H. Briggs, and R. H. Locker.

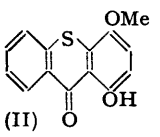
The relation between the constitution of some related flavonol derivatives and the properties listed in the title is discussed.

During the work described in this series of papers we have recorded the solubility of various flavonols in sodium hydrogen carbonate, sodium carbonate, and sodium hydroxide solutions, and in concentrated sulphuric and hydrochloric acids, their colours with ferric chloride, and their ultra-violet absorption spectra in alcoholic solution. From these observations a number of useful general conclusions may be made.

In Table I are listed the solubilities in concentrated hydrochloric acid and alkalis and the ferric chloride colours of some flavonols, mostly related to this series.

Acidity.—The 5-hydroxyflavonols (9—12) are outstanding by virtue of their insolubility in aqueous alkalis (for further examples see Part VI, preceding paper). 3-Hydroxyflavones also tend to be sparingly soluble (cf. 17 and further examples cited in Part VI). This, however, is not due to their lack of acidity but simply to the fact that their sodium salts are insoluble in water. Ethereal solutions of (9—12) are, however, unaffected by sodium carbonate and


(I)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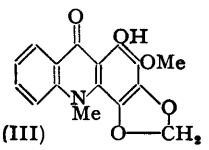
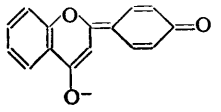

(III)

hydrogen carbonate solutions, thus manifesting their weak acidic properties, as is to be expected because of hydrogen bonding between the 4- or the 5-hydroxyl group and the carbonyl group as in (I).

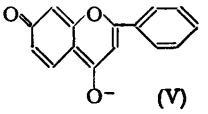
* Part VI, preceding paper.

A similar effect is observed with 1-hydroxy-4-methoxy-10-thioxanthone (II) which contains the same group (Roberts and Smiles, *J.*, 1929, 1322) and with the nor-alkaloids of the melicopine series, *e.g.*, normelicopine (III) (Crow and Price, *Australian J. Sci. Res.*, 1949, **2**, *A*, 255, 282) which are also insoluble in alkalis.

It is possible that the strong acidity of 4′-hydroxyflavonols, *e.g.*, (18), may be due to resonance of its ion with the form (IV), the further stability of the ion enhancing the acidic properties. This is supported by the fact that where hydrogen bonding occurs between the carbonyl group and the 5-hydroxyl group such resonance is no longer possible and the acidic properties are reduced, cf. (6) and (18). A similar resonance (cf. V) is possible with the



(IV)



(V)

7-hydroxyflavonol (15) but its acidity, as shown by its solubility in sodium carbonate solution, is not recorded. However, from a comparison of the compounds (1)—(4) it appears that the 7-hydroxyl group also confers strong acidity on the molecule. Resonance is also possible with

TABLE I.

Properties of flavonols.

No.	Substituents: OH	OMe	OEt	O_2CH_2	Solubility in: Satd. $NaHCO_3$	2N-Na_2CO_3	2N-NaOH	Conc. HCl	Colour in $FeCl_3$
1	3 : 5 : 7 : 3′ : 4′	—	—	—	(+)	+	+	—	+
2	3 : 5 : 3′ : 4′	7	—	—	—	+	+	—	+
3	3 : 5 : 4′	7 : 3′	—	—	—	+	+	—	+
4	5 : 7 : 4′	3 : 3′	—	—	(+)	+	+	—	+
5	5 : 7 : 8	3	—	3′ : 4′	(+)	+	+	—	+
6	5 : 4′	3 : 7 : 3′	—	—	—	—	+	—	+
7	5 : 4′	3 : 7 : 8 : 3′-	—	—	—	—	+	—	+
8	5 : 7	3	—	3′ : 4′	—	—	+	—	+
9[a]	5	3 : 7 : 3′ : 4′	—	—	—	—	—	—	+
10[a]	5	3 : 7	—	3′ : 4′	—	—	—	—	+
11[b]	5	3 : 6 : 7	—	3′ : 4′	—	—	—	—	+
12[a]	5	3	—	6 : 7 : 3′ : 4′	—	—	—	—	+
13	6	3 : 5 : 7	—	3′ : 4′	—	—	+	+	—
14	6	3 : 5	7	3′ : 4′	—	—	+	+	—
15	7	3 : 5 : 8 : 3′ : 4′	—	—	—	?	+	+	—
16	8	3 : 5 : 7 : 3′ : 4′	—	—	—	?	+	?	+
17	3	5 : 7 : 8 : 3′ : 4′	—	—	—	—	(+)	?	+
18	4′	3 : 5 : 7 : 3′	—	—	—	+	+	+	—

\+ Soluble or, with $FeCl_3$, a brown or green colour. (+) Slightly soluble.
— Insoluble or, with $FeCl_3$, no colour. ? Not recorded.

[a] These compounds are insoluble in sodium hydroxide but, when dissolved in ether, react with sodium hydroxide solution to form an insoluble sodium salt at the interface. Carbonate and bicarbonate solutions are without action on the ethereal solutions.

[b] This compound is insoluble in sodium hydroxide solution and practically insoluble in ether. The very dilute solution formed in the latter case produces a yellow colour with sodium hydroxide solution but not with carbonate or bicarbonate solution.

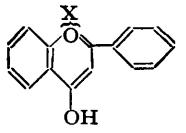
References : 1, Rigaud, *Annalen*, 1854, **90**, 294, and our own observations. 2, Liebermann and Hörmann, *ibid.*, 1879, **196**, 313, and our own observations. 3, Perkin and Geldard, *J.*, 1895, **67**, 498, and our own observations. 4, 6, 18, *J.*, 1950, 864. 5, 8, 10, *J.*, 1949, 2162. 7, *J.*, 1949, 2157; 1950, 864. 9, Our own observations. 11, *J.*, 1950, 2376, 2379. 12, Preceding paper. 13, *J.*, 1950, 2379, and preceding paper. 14, *J.*, 1949, 2157, and preceding paper. 15, Baker, Nodzu, and Robinson, *J.*, 1929, 74. 16, 17, Rao and Seshadri, *Proc. Indian Acad. Sci.*, 1946, **24**, *A*, 375.

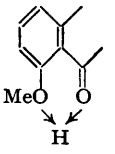
the 5-hydroxyl compounds, but here apparently hydrogen bonding appears to be the dominating factor. The very high acidities of (1) and (4) may be due to the fact that both resonant forms (IV) and (V) are possible, giving still greater stabilisation of the ion. We have observed in the hydroxyanthraquinone series that the polarographic half-wave potentials increase with increasing dissociation constants (forthcoming communication) and in harmony with our observations is that of Geissman *et al.* (*J. Amer. Chem. Soc.*, 1947, **69**, 155) that the polarographic half-wave

potentials, in alkaline solution, of flavonols with free 5-, 7-, and 4′-hydroxyl groups are considerably higher than those in which these positions are methylated.

A hydroxyl group on $C_{(8)}$ apparently does not confer any marked acidity, cf. (13) and (14). A comparison of (5) and (8) shows that one 8-hydroxyl group may lead to increased acidity but it should be noted that 4′-benzyloxy-5 : 7 : 8-trihydroxy-3 : 3′-dimethoxyflavone, like its corresponding 5 : 7-dihydroxy-analogue (Part III, *J.*, 1950, 864), is insoluble in sodium carbonate solution.

Basicity.—All the flavonols obtained during this series of investigations are soluble in concentrated sulphuric acid, giving intensely yellow solutions, and the fully alkylated flavonols are also soluble in concentrated hydrochloric acid, affording similar solutions (cf. *J.*, 1949, 2157, for the preparation of various salts of meliternatin and meliternin, which are decomposed when heated or, instantly, by water). The yellow colour of a solution of meliternatin in concentrated hydrochloric acid disappears on dilution with two volumes of water, and the flavonol is precipitated. The salts of quercetin pentamethyl ether are rather more stable.

(VI) 

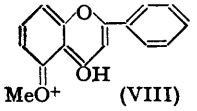
 (VII)

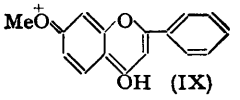
It may be seen from the table that a free 6-, 7-, or 4′-hydroxyl group does not prevent dissolution in hydrochloric acid, but all the flavonols containing a free 5-hydroxyl group are insoluble.

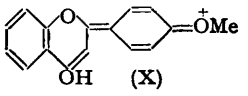
The mechanism of salt formation with γ-pyrone derivatives is still controversial, one view being that they have a benzenoid structure (VI) (cf. Hunter and Partington, *J.*, 1933, 87).

Roberts *et al.* have found (*J.*, 1929, 863, 1322; 1931, 520; 1932, 1792, 1982) that certain methoxyxanthones, methoxy-10-thioxanthones, and αα′-dimethoxyanthraquinones dissolve readily in concentrated hydrochloric acid, giving salts which are decomposed by water. They observed that whereas 1-methoxy-10-thioxanthones and 1-methoxyxanthones showed a much greater tendency towards salt formation than other derivatives, 1-hydroxy-4-methoxyxanthone was insoluble in concentrated hydrochloric acid. These properties very closely parallel those of the 5-methoxy- and 5-hydroxy-flavonols of the present investigation.

The effect of the 1-methoxyl group in the salt formation of xanthones was attributed to chelation of the type (VII). Perhaps a more satisfactory explanation for this increased basicity and the more intense colour is that further resonant ions are possible, in the case of flavones, with 5- as well as 7- and 4′-methoxy-derivatives, *e.g.*, the forms (VIII), (IX), and (X) respectively, in addition to those derived from (VI). Since flavonol derivatives with all their phenolic groups free do form salts it appears that the form (VI) must at least be one of the contributing structures.

 (VIII)

 (IX)

 (X)

Further evidence for the intimate association of a neighbouring methoxyl group with salt formation is the fact that heating 1-methoxyxanthones in concentrated hydrochloric acid causes selective demethylation in the 1-position. A similar effect is observed in the *Melicope* alkaloids (Crow and Price, *loc. cit.*). These weakly basic *N*-methylacridones, which are nitrogen analogues of the xanthones, also form mineral-acid salts which are largely hydrolysed in water. Heating the dry hydrochloride, or refluxing it with alcoholic hydrochloric acid, causes demethylation in the 1-position. The resulting nor-alkaloids are even weaker bases than the parent compounds and are also insoluble in alkali (cf. the section on acidity). It appears that with these alkaloids salt formation could be a function of the oxygen rather than of the nitrogen atoms.

Ferric Chloride Colours.—It may be seen from the table that the production of a colour with ferric chloride solution (carried out by the addition of aqueous ferric chloride to an alcoholic solution of the flavone) is a property of 3-, 5-, or 8-hydroxy-compounds (for further

details relating to 3- and 5-hydroxy-compounds see the preceding paper) but not of 6-, 7-, or 4'-hydroxy-derivatives (cf. also, for 6-hydroxyflavones, Seshadri and his co-workers, *Proc. Indian Acad. Sci.*, 1945, **21**, 159; 1945, **22**, 301, 302; 1946, **23**, 274; 1946, **24**, 233, 241; 1947, **26**, 187; for 7-hydroxyflavones, *idem, ibid.*, 1941, **14**, 290; 1945, **22**, 160; 1946, **24**, 377, 457;

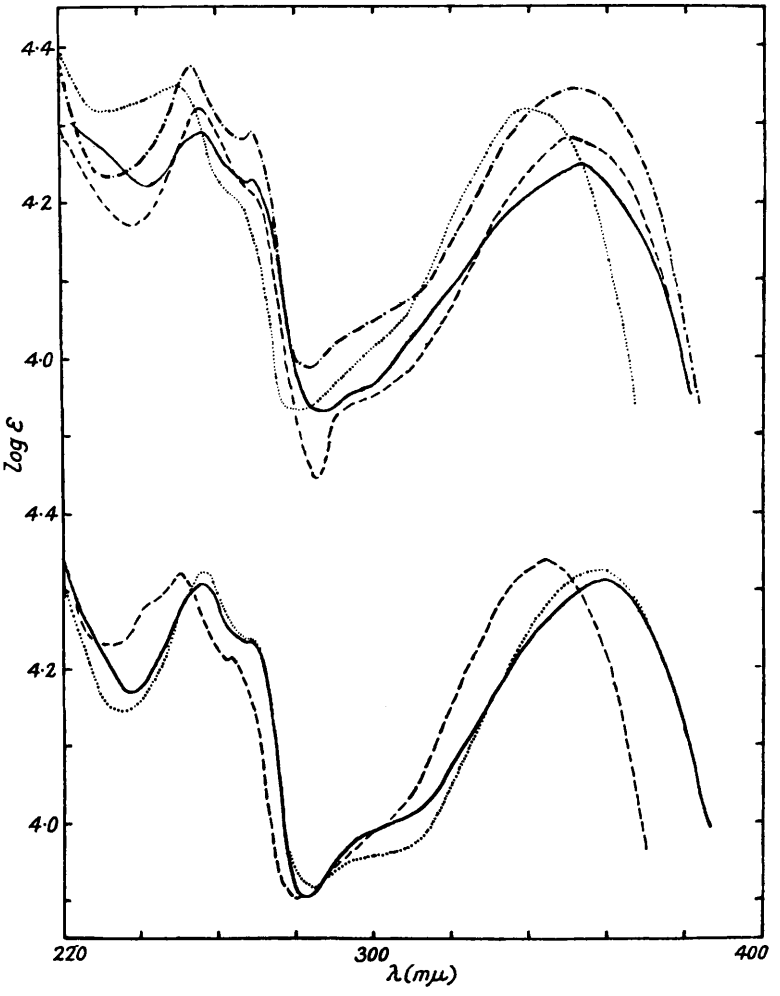


FIG. 1.

FIG. 2.

FIG. 1.

— · — · — · — 5-*Hydroxy*-3 : 7 : 3' : 4'-*tetramethoxyflavone* (A6).
———— 5 : 7-*Dihydroxy*-3-*methoxy*-3' : 4'-*methylenedioxyflavone* (A4).
– – – – – – – – – 5-*Hydroxy*-3 : 7-*dimethoxy*-3' : 4'-*methylenedioxyflavone* (A5).
. . . . . 3 : 5 : 7-*Trimethoxy*-3' : 4'-*methylenedioxyflavone* (iso*kanugin*) (A7).

FIG. 2.

. . . . . 5 : 7 : 4'-*Trihydroxy*-3 : 3'-*dimethoxyflavone* (A8).
———— 5 : 4'-*Dihydroxy*-3 : 7 : 3'-*trimethoxyflavone* (A9).
– – – – – – – – – 4'-*Hydroxy*-3 : 5 : 7 : 3'-*tetramethoxyflavone* (A10).

1949, **30**, 158; for 4'-hydroxyflavones, *idem, ibid.*, 1946, **24**, 457; *J.*, 1946, 771; 1947, 122). These properties afford valuable structural evidence in support of degradative experiments.

Absorption Spectra.—The ultra-violet absorption spectra of natural and synthetic flavonols obtained in this series of investigations together with a few related compounds are recorded in Figs. 1—5 and in Table II. Unless stated otherwise all spectra were measured in *ca.* M/20,000

alcoholic solutions with a Beckman spectrophotometer, Model D.U. The average accuracy of $\lambda_{max.}$ is *ca.* ±1 mμ, that of log $\varepsilon_{max.}$ *ca.* ±0·01. Some of these results have already been recorded in Part I (*loc. cit.*) and Part II (*J.*, 1949, 2162).*

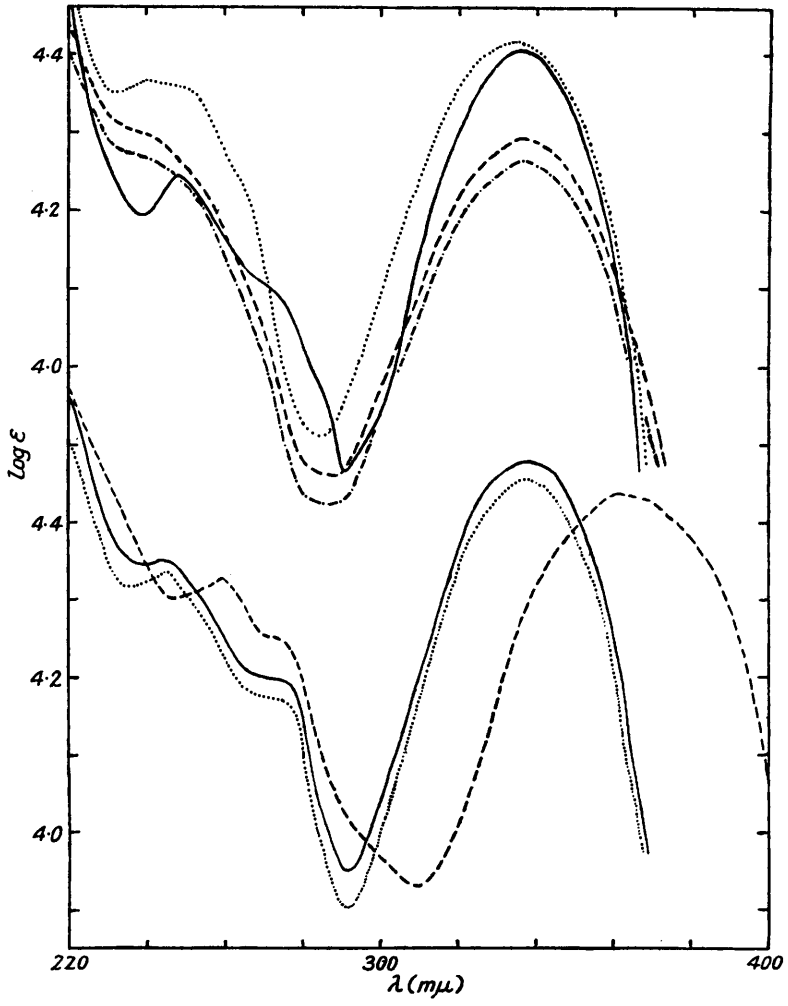


FIG. 3.

FIG. 4.

FIG. 3.

. . . . . *Quercetagetin hexamethyl ether* (A14).
———— *Meliternatin* (A13).
— · — · — · — *Melisimplexin* (*natural*) A11).
– – – – – – – – *Melisimplexin* (*synthetic*) (A12).

FIG. 4.

– – – – – – – – *Quercetagetin* (A17).
. . . . . 6-*Hydroxy*-3 : 5 : 7-*trimethoxy*-3′ : 4′-*methylenedioxyflavone* (A15).
———— 7-*Ethoxy*-6-*hydroxy*-3 : 5-*dimethoxy*-3′ : 4′-*methylenedioxyflavone* (A16).

The general pattern of the peaks is fairly constant. In most cases there are two pronounced peaks, at *ca.* 250 (band I) and *ca.* 350 mμ (band III), with a less pronounced peak or point of inflexion at *ca.* 270 mμ (band II).

* The present values are somewhat different from those previously recorded and are the more accurate. Also, owing to an unfortunate interchange of samples, the values already recorded for quercetagetin hexamethyl ether and 5 : 7-dihydroxy-3-methoxy-3′ : 4′-methylenedioxyflavone should be interchanged and slightly amended (as now presented).

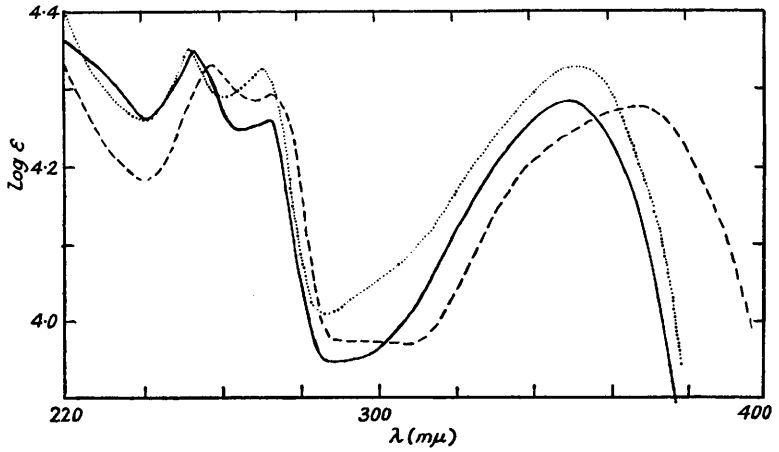


FIG. 5.

. . . . . *Gossypetin hexamethyl ether* (A20).
———— *Meliternin* (A18).
– – – – – – – – – – *Ternatin* (A21)

(a) *Quercetin derivatives* (Figs. I and II). The measurements of quercetin, quercitrin, and rhamnazin were made by Mr. J. Mills, University of Adelaide, through the courtesy of Professor A. Killen Macbeth, on a Hilger instrument. In these cases no band or inflexion is recorded corresponding to band II (which is present in all other quercetin derivatives) but this is probably due to use of an instrument of lower resolving power.

TABLE II.

		$\lambda_{max.}$	log ε	$\lambda_{max.}$	log ε	$\lambda_{max.}$	log ε
A1	Quercetin	258	4·32	—	—	375	4·34
A2	Quercitrin (3-rhamnoside)	260	4·35	—	—	352	4·24
A3	Rhamnazin (3 : 5 : 4′-trihydroxy-7 : 3′-dimethoxyflavone)	255	4·37	—	—	375	3·27
A4	5 : 7-Dihydroxy-3-methoxy-3′ : 4′-methylenedioxyflavone	256	4·29	269	4·23	353	4·25
A5	5-Hydroxy-3 : 7-dimethoxy-3′ : 4′-methylenedioxyflavone	255	4·32	269 *	4·21	353	4·28
A6	5-Hydroxy-3 : 7 : 3′ : 4′-tetramethoxyflavone (quercetin tetramethyl ether)	254	4·37	269	4·29	352	4·34
A7	3 : 5 : 7-Trimethoxy-3′ : 4′-methylenedioxyflavone	250	4·35	263 *	4·21	340	4·32
A8	5 : 7 : 4′-Trihydroxy-3 : 3′-dimethoxyflavone	256	4·31	268	4·24	360	4·31
A9	5 : 4′-Dihydroxy-3 : 7 : 3′-trimethoxyflavone	257	4·32	268	4·24	360	4·33
A10	4′-Hydroxy-3 : 5 : 7 : 3′-tetramethoxyflavone	251	4·32	263	4·22	345	4·34
A11	Melisimplexin (natural)	235	4·27	—	—	336	4·26
A12	Melisimplexin (synthetic)	235	4·30	—	—	336	4·29
A13	Meliternatin	248	4·25	269 *	4·11	336	4·41
A14	Quercetagetin hexamethyl ether	240	4·37	—	—	335	4·42
A15	6-Hydroxy-3 : 5 : 7-trimethoxy-3′ : 4′-methylenedioxyflavone	245	4·24	272 *	4·07	337	4·35
A16	7-Ethoxy-6-hydroxy-3 : 5-dimethoxy-3′ : 4′-methylenedioxyflavone	244	4·25	272 *	4·10	337	4·38
A17	Quercetagetin	259	4·23	272 *	4·15	361	4·34
A18	Meliternin (natural)	253	4·35	273	4·26	351	4·29
A19	Meliternin (synthetic)	253	4·36	272	4·27	351	4·29
A20	Gossypetin hexamethyl ether	252	4·34	271	4·33	351	4·33
A21	Ternatin	258	4·33	273	4·29	368	4·28

* Point of inflexion. N.B. The absorption spectrum of melisimplin and 5-hydroxy-3-methoxy-6 : 7 : 3′ : 4′-dimethylenedioxyflavone (preceding paper) could not be included in this survey owing to the insolubility of the substances in alcohol and other suitable solvents.

References: A1, Cf. Grinbaumówna and Marchlewski, *Biochem. Z.*, 1937, **290**, 261. A2, Mayer and Cook, " The Chemistry of Natural Coloring Matters," Reinhold Publ. Corp., 1943, p. 188. A3, *Op. cit.*, p. 190. A4, 5, 7 (*iso*kanugin), 19, *J.*, 1949, 2162. A6, Herzig, *Monatsh.*, 1884, **5**, 72. A8, 9, 10, *J.*, 1950, 864. A11, *J.*, 1950, 2376, 2379. A12, *J.*, 1950, 2379. A13, 14, 18, 20, *J.*, 1949, 2157. A15, Preceding paper. A16, *J.*, 1949, 2157, and preceding paper. A17, Baker, Nodzu, and Robinson, *J.*, 1929, 74. A21, *J.*, 1949, 2157; 1950, 864.

A low-intensity inflexion at *ca.* 300 mμ is a common feature of these derivatives not shared by quercetagetin or gossypetin derivatives.

Band I of quercetin agrees fairly well with the same band of its derivatives, but band III lies considerably further towards the visible spectrum. Substitution at $C_{(3)}$ with a rhamnose unit (A2; this and similar numbers refer to Table II) has little effect on band I but causes a sharp bathochromic displacement of 23 mμ in band III. The combined effect of methylation of the 7- and the 3′-position (A3) is small in band I and zero in band III. Methylation of the 7-position alone does not affect $\lambda_{max.}$ within experimental error (cf. A4–5 and A8–9), whereas methylation of the 4′-position only causes a small displacement (5 mμ) of band III towards the shorter wave-lengths (cf. A7 and 10).

The greatest effect is caused by methylation of the 5-hydroxyl group, which displaces all the bands, particularly band III, towards the shorter wave-lengths (cf. A2–4 and A6–7). The replacement of two vicinal methoxyl groups by a methylenedioxy-group does not affect $\lambda_{max.}$ by more than the experimental error. Band II is remarkably constant at 269 mμ, being affected only by methylation of the 5-hydroxyl group.

(b) *Quercetagetin derivatives* (Figs. III and IV). For these substances band I is present as a peak or an inflexion, band II is an inflexion or is missing, and band III forms a peak of high intensity. With these derivatives replacement of vicinal methoxyl groups by methylenedioxy-groups in either the benzo-nucleus or the side phenyl group considerably changes $\lambda_{max.}$ for band I (cf. A11–14). Methylation of the 6-position causes a 10-mμ bathochromic shift in band I. As expected, substitution of a methoxyl group by an ethoxyl group at $C_{(7)}$ makes practically no difference to the absorption. It is surprising that melisimplexin, intermediate in structure between quercetagetin hexamethyl ether and meliternatin, should have log $\varepsilon_{max.}$ for band III *ca.* 0·13 lower than either of these.

(c) *Gossypetin derivatives* (Fig. 5). Since the curves of natural and synthetic meliternin correspond within experimental error only that of the natural product is reproduced. The similarity in the structures of meliternin and gossypetin hexamethyl ether is reflected in their similar absorption curves. The free 5-hydroxyl group in ternatin, as expected, causes a 6-mμ shift in band I towards longer wave-lengths (cf. the quercetin derivatives), band II is unaltered, and the shift of 17 mμ in band III corresponds, within experimental error, with the sum of displacements due to 4′- and 5-hydroxyl groups in the quercetin series.

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